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Physiological analyses of the afferents controlling brain neurochemical systems

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These experiments are directed at the neurochemical systems and neuroanatomical pathways that control the activity of brain serotonergic (dorsal raphe nucleus) and noradrenergic (locus coeruleus) neurons. It seeks to answer these questions by studying single unit activity in combination with microiontophoresis in the awake cat during exposure to physiologically relevant conditions. Four series of studies are proposed, the first three will examine the neurochemical afferents that control the following types of activity of serotonergic and noradrenergic neurons: 1) tonic, as well as state-dependent activity; 2) phasic activity evoked by various sensory stimuli; and 3) activation in response to environmental and physiological challenges (stressors). The fourth series of studies will take results from the first three and seek to establish the nuclear site of origin of these effects by employing electrical stimulation in combination with single unit recording and microiontophoresis. This research program will provide a critical link for understanding the control of these two important neurochemical systems, and will thus help to elucidate, more broadly, their role in processes such as state-dependent changes in physiology and behavior, and arousal and attention.

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February 24, 1992

Dr. Genevieve Haddad
Life Sciences Directorate
Department of the Air Force
AFOSR
Bolling Air Force Base, DC 20332-6448

Dear Dr. Haddad:

The brief narrative in this letter plus the enclosed papers constitutes my Annual Technical Report for my AFOSR grant (90-0294).

The goal of our AFOSR research is to take the next logical step in our understanding of the function of modulatory chemical neurotransmitters in the mammalian brain. Prior to this, we and others had gathered a great deal of information about the electrophysiological activity of brainstem monoaminergic (serotonergic, noradrenergic, and dopaminergic) neurons. Additionally, a great deal of information was known about the action of these neurotransmitters upon the activity of their postsynaptic target neurons, such as those in the cerebral cortex.

Within this context, we are asking two fundamental questions. First, what are the neurochemical afferents that control the activity of the monoaminergic neurons themselves? For example, we know that serotonergic neurons can be activated by phasic sensory stimuli, and that they dramatically decrease their activity during sleep. However, we have no information regarding the neurochemical inputs that mediate these increases and decreases in neuronal activity. Second, although we have a general sense of how norepinephrine and serotonin influence their target neurons, the critical issues of how and when this occurs under physiological conditions remains obscure.

We address these questions by bringing together two well-known approaches that have typically been used separately: microiontophoresis and single unit recordings in conscious animals. Specifically, we examine extracellularly recorded action potentials in combination with the microiontophoretic application of neurotransmitter agonists or antagonists in awake, head-restrained cats. This allows us to examine questions in the absence of any confounding influences of anesthesia, and to ask these questions in the intact animal under physiologically-relevant conditions.

We have made substantial progress on the first issue and have written two manuscripts on this work (one a methodological paper, in press, and, the other, an empirical report of the results). We found that we could block the activation of serotonergic neurons by phasic sensory stimuli through the iontophoretic application of excitatory amino acid (EAA) antagonists. Importantly, these effects were seen in the absence of any change in the spontaneous or basal activity of these neurons. We also found that we could restore the decreased activity of a serotonergic neuron during sleep to its waking level by iontophoretically applying a GABA antagonist. Once again, the specificity of this effect is demonstrated by the fact that the same amount of antagonist had no neuronal effect when applied during waking. Thus, these data indicate that under physiologically relevant conditions an EAA input can be activated by phasic sensory stimuli and thereby increase the discharge of serotonergic neurons, while a tonic GABAergic input exerted during sleep can suppress the activity of these neurons.

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Experiments on the second issue are just beginning to bear fruit. We are asking how the response of somatosensory neurons in the cat cortex, which are normally activated by movement of muzzle whiskers, can be modulated by variables such as behavioral state, arousal, and attention, and further, what neurochemical afferent inputs mediate these changes? These studies are similar to those described above, where we determined which neurochemical inputs were exerting their effect upon serotonergic neurons by microiontophoretically applying neurotransmitter agonists and antagonists during specific environmental or physiological conditions.

I hope you find these materials useful, and I apologize for being late with this report. I look forward to continued interactions with you and Dr. Berry, and thank you for your continued support of our research program.

Sincerely,

Barry L. Jacobs
Professor and Director
Program in Neuroscience

BLJ:ack
Enclosures

P.S. I look forward to your visiting our new laboratory in the coming months.